II. Remarks

A. Status of the Claims

Claims 76-84 and 88-89 are pending in this application. The claims have not been amended in this response.

B. Rejection under 35 U.S.C. § 103

In the Office Action, claims 76-84 and 88-89 were rejected under 35 U.S.C. 103(a) "as being unpatentable over US Patent 5,837,379 to Chen et al. by itself or in view of Cheng et al. (Evaluation of Sustained/Controlled Release dosage forms of 3-Hydroxy-3-Methylglutaryl-Coenzyme A (HMG-CoA) Reductase Inhibitors in Dogs and Humans, Pharmaceutical Research (1993), 10:1683-1687)."

1. Rejection over Chen et al.

This rejection is traversed. It is again respectfully submitted that Chen et al. is directed to controlled release dosage forms and only incidentally mentions lovastatin in an exhaustive list (see column 2, line 51 to column 3, line 11 of Chen et al.) of over one hundred possible agents including various classes of drugs and specific drugs in multiple forms (e.g., salts, esters, etc.). The only data provided in this patent directed to in-vivo results is data directed to dosage forms of nifedipine, which is not in any way related to lovastatin. None of the exemplified formulations includes lovastatin, and no information is provided in this reference concerning a desired time to maximum plasma concentration for any drug, let alone lovastatin. Further, there is no statement in Chen et al. relating to T_{max}, and there is no suggestion in Chen et al. that the *in vivo* plasma levels achieved in the examples of the reference would be desirable for controlled or sustained release formulations containing lovastatin. Therefore, there is no motivation in Chen et al. to produce dosage forms of lovastatin having the claimed pharmacokinetic parameters.

It is again respectfully submitted that one skilled in the art would not be motivated to select the particular claimed agent (i.e., lovastatin) from the large genus disclosed at column 2, line 51 to column 3, line 11 of Chen et al.

Although the Examiner states that she has not purported that nifedipine and lovastatin have similar structures, but that the controlled release device taught by Chen et al is similar, if not the same as the instantly claimed device, it is respectfully submitted that the differences in structure, pharmacological properties, and characteristics of the species of active agent would be considered by one or ordinary skill in the art in the preparation of a controlled release formulation. Any teaching or suggestion in the reference of a preferred species that is significantly different in structure from the claimed species weigh against selecting the later selected species. See, e.g., *In re Baird*, 16 F.3d 382-83, 29 USPQ2d 1552 (Fed. Cir. 1994). Accordingly, the examples of Chen et al. directed to a compound (i.e. nifedipine) that is not structurally similar to lovastatin (as discussed above) is further evidence that one skilled in the art would not be motivated to select lovastatin from the genus described therein.

The broad ranges described in the present specification at Table 1 provide guidance to one of ordinary skill in the art to prepare a dosage form of the present invention with routine experimentation. One skilled in the art would appreciate that formulations of lovastatin could be prepared that do not meet the limitations of claim 1, but would generically fall with the ranges of Table 1 of the present application.

It is respectfully submitted that Chen et al. fail in the very least to teach, hint or suggest the T_{max} range recited in the present claims as no information is provided in the reference concerning a desired time to maximum plasma concentration (T_{max}) for any drug, let alone lovastatin. Further, there is no statement in Chen et al. relating to T_{max}, and there is no suggestion in Chen et al. that a particular T_{max} would be desirable for controlled release formulations containing lovastatin. In addition, Chen et al. fail to teach or suggest a controlled release oral solid dosage form which increases the bioavailability of an active agent as compared to the same amount of the active agent administered in an

immediate release form as recited in present claim 76 (with respect to lovastatin). In addition, there is no information contained in Chen et al. regarding any pharmacokinetic values with respect to lovastatin, nor is there any mention of lovastatin acid in Chen et al.

Therefore, as Chen et al. fails to teach or suggest the presently claimed invention, the Examiner is respectfully requested to withdraw this rejection.

2. Rejection over Chen et al. in combination with Cheng et al (hereinafter "the Cheng reference").

This rejection is also traversed. It is respectfully submitted that the Cheng reference fails in the very least to cure the deficiencies of Chen et al. discussed above. In particular, the formulations of the Cheng reference describe controlled release lovastatin formulations which provide a *decreased bioavailability* of lovastatin as compared to an immediate release formulation in dogs. This is evident in Table II of the Cheng reference which reports the bioavailability of controlled release formulations (CRS8 and CRS14) as compared to an immediate release formulation (CT) as follows:

Immediate Release (CT)	901±161
Controlled Release (CRS8)	418±180
Controlled Release (CRS14)	487±181

As set forth above, the data for the lovastatin controlled release formulations of the Cheng reference demonstrate a decrease of 54%(CRS8) and 46%(CRS14). Even taking the low end of the standard deviation for the immediate release and the high end of the standard deviation for the controlled release formulations demonstrates a decrease of 19%(CRS8) and 10%(CRS14). This data is in direct contrast to the claimed dosage forms, which increase the bioavailability of lovastatin as compared to immediate release dosage forms. It is respectfully submitted that formulations SRT8 and SRT14 are not relevant to this issue as the Cheng reference states in the last paragraph on page 1685 that

"[b]ecause the SRT8 and SRT14 dosage forms showed little evidence of *in vivo* sustained-release functionality, they were dropped from further consideration."

Moreover, when lovastatin is administered, the Cheng reference does not teach or suggest the claimed Tmax range. For example, the Tmax values reported in the Cheng reference for the sustained and controlled-release formulations of lovastatin after administration to dogs are as follows: SRT8 had a Tmax of 1.8±0.4; SRT14 had a Tmax of 2.3±0.8; CRS8 had a Tmax of 4.0±0.0; and CRS14 had a Tmax of 7.5±1.2.

It is the Applicant's position that if dog data is instructive with respect to humans, the Cheng reference does not teach or suggest the claimed bioavailability parameter or Tmax in humans in view of the above data. Alternatively, if dog data is not instructive with respect to humans, Cheng still does not teach or suggest the claimed parameters.

Therefore, as the Cheng reference fails to cure the deficiencies of Chen et al., the Examiner is requested to withdraw this rejection.

C. Double Patenting Rejections

Claims 76-87 were rejected for obviousness-type double patenting over claims 1-12 of U.S. Patent No. 5,916,595, claims 1 and 4-14 of U.S. Patent No. 6,485,748, and claims 1, 4-13, and 15 of U.S. Patent No. 5,837,379.

1. U.S. Patent Nos. 5,916,595

In response to the obviousness-type double patenting rejection over claims 1-12 of U.S. Patent No. 5,916,595, a terminal disclaimer over this patent is filed herewith. Applicants acknowledged that the terminal disclaimer was inadvertently omitted in the last response, and it submitted herewith.

Applicants note that the obviation of an obvious-type double patenting rejection by the filing of a terminal disclaimer is not an admission, acquiescence, or estoppel on the merits of an issue of obviousness. *See Quad Environmental Technologies Corp. v.*

Union Sanitary District, 946 F.2d 870, 873-74, 20 U.S.P.Q.2d 1392, 1394-95 (Fed. Cir. 1991).

2. U.S. Patent Nos. 6,485,748

The rejection of claim 76-87 over claims 1-12 of U.S. Patent No. 6,485,748 is traversed. Applicants note that when considering when the invention defined in the claim of an application is an obvious variation of the invention defined in the invention of a patent, the disclosure of the patent may not be used a prior art. However, the specification can be used as a dictionary to learn the meaning of a term in the patent claim, or be examined with respect to those portions which provide support for the claims (See MPEP 8th Edition, Revision 2, Section 804(2)(B)(1)).

It is respectfully submitted that the claims of the '748 patent patents fail in the very least to teach, hint or suggest the T_{max} range recited in the present claims. It is also respectfully submitted that the claims of the '748 patent fail to teach or suggest a controlled release dosage form comprising lovastatin wherein the dosage form increases the bioavailability of lovastatin and does not increase the bioavailability of lovastain acid, as compared to the same amount of lovastatin administered in an immediate release dosage form as presently claimed.

In addition, the specification of the '748 patent, like that of the Chen et al. '379 patent, only incidentally mentions lovastatin in an exhaustive list (see column 2, line 58 to column 3, line 16 of the '748 patent) of over one hundred possible agents including various classes of drugs and specific drugs in multiple forms (e.g., salts, esters, etc.). The only *in vivo* data provided in the '748 patent is data directed to dosage forms of nifedipine, which is not in any way related to lovastatin, as described above. None of the exemplified formulations includes a drug that is lovastatin, and no information is provided in this reference concerning a desired time to maximum plasma concentration for any drug, let alone lovastatin. Moreover, there is no statement in either the specification or the claims of the '748 patent relating to T_{max}, or suggestion that the *in*

vivo plasma levels achieved in the examples of the reference would be desirable for controlled or sustained release formulations containing lovastatin.

It is respectfully submitted that it is only with the benefit of the disclosure of the present application, that one skilled in the art would be motivated to prepare a formulation that provides a time to maximum plasma concentration (T_{max}) as recited in the present claims. Accordingly, the Examiner is using impermissible hindsight reasoning in making this rejection.

3. U.S. Patent No. 5,837,379 (Chen et al.)

The rejection of claim 76-84, 88-89 over claims 1, 4-13, and 15 of U.S. Patent No. 5,837,379 (Chen et al.) is traversed. This rejection is traversed. For similar reasons as discussed above with respect to the 35 U.S.C. 103 rejection of the present claims over Chen et al., it is respectfully submitted that the claims of the '379 patent fail to teach or suggest the T_{max} range recited in the present claims as no information is provided in the claims concerning a desired time to maximum plasma concentration (T_{max}) for any drug, let alone lovastatin. In addition, the claims of Chen et al. fail to teach or suggest a controlled release oral solid dosage form which increases the bioavailability of an active agent as compared to the same amount of the active agent administered in an immediate release form as recited in present claim 76 (with respect to lovastatin).

In view of the terminal disclaimer filed herewith with respect to the '595 patent and the arguments presented with respect to the '748 patent and the '379 patent, Applicants respectfully request that these obviousness-type double patenting rejections be removed.

III. Conclusion

It is now believed that the above-referenced rejections have been obviated and it is respectfully requested that the rejections be withdrawn.

It is believed that no fee is due for this response. If it is determined that any fee is due, the Examiner is specifically authorized to charge said fee to Deposit Account No. 50-0552.

An early and favorable action on the merits is earnestly solicited.

Respectfully submitted,
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